Remarks

Specification:

Applicants have amended the specification as suggested in the Office Action. Replacement pages have been submitted incorporating the changes.

Rejection of claims under 35 U.S.C. 112:

Claims 1-3 and 3-39 were rejected under §112 as not being enabling for the methods claimed.

Applicants have amended independent claims 1 and 39 to clarify the method of delivery and the target cells. On page 5, paragraph 2, "The specification does not teach targeting any parenchymal cell other than skeletal muscle cells." The claims have thus been amended to specify delivery of polynucleotides to skeletal muscle cells as well as to clearly indicate the blood vessel into which the polynucleotide is injected and the skeletal muscle cells to which the polynucleotide is delivered. The amended claims further clarify the method of impeding blood flow as well as the location of the injection and the target cells relative to the placement of the blood vessel occlusion. Teachings and support for an external device for occluding blood vessels are given on page 3 lines 8-11, page 5 lines 7-8, and page 5 lines 13-24 and in the examples of the specification.

The applicants respectfully disagree with the examiner concerning the terms anterior, posterior and superficial muscle cells. These are terms of art that specify the location of the muscle relative to its position in the mammal itself, and not to the position of the mammal relative to a viewer. However, the applicants have canceled claims 10, 15, 23, and 27 concerning deep or interior muscle cells and have amended claims 11 and 12 to remove the ambiguous abbreviations.

Applicants have either cancelled or amended the claims to obviate the rejections. Applicants respectfully request that the §112 rejections be removed.

Rejection of claims under 35 U.S.C. 102:

Claims 1-32 and 37-39 were rejected under §102(b) as being anticipated by Milas, Sferra and Nabel. Milas and Sferra teach adenoviral delivery to hepatocytes and intestinal cells, respectively. Nabel teaches delivery exclusively to vascular cells, immune cells and vessel smooth muscle cells. As noted above, Applicants have amended the claims to specify delivery to limb skeletal muscle cells.

Claims 1-3, 8-10, 13-15, 32, and 38-39 were rejected under §102(e) as being anticipated by Wolff. Wolff taught injection of polynucleotide into heart interstitium, which the examiner considers a vessel that contains blood. The amended claims more clearly specify injection of the polynucleotide into a limb blood vessel and delivery to limb skeletal muscle cells.

Applicants believe that the amended claims obviate the rejections since the prior art does not teach the use of a noninvasive external device to aid in the delivery of polynucleotides to limb skeletal muscle cells. In fact, as the examiner notes on page 5, both Milas and Yc, failed to observe delivery of polynucleotide to muscle cells after injection of adenovirus into the femoral artery or the retroorbital venous plexus (Milas et al 1997, page 2201 column 2, line

16-18; Ye et al 2000, page 623, column 2, lines 16-18). Rather, both researchers observed delivery to liver. In contrast, applicants have clearly shown delivery of polynucleotides to skeletal muscle using the claimed processes, see examples 1 & 3 (primate), and examples 5, 7, 8, 9 and 10 (rat).

The Examiner's objections and rejections are now believed to be overcome by this response to the Office Action. In view of Applicants' amendment and arguments, it is submitted that claims 1-4, 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39-40 should be allowable and Applicants respectfully requests an early notice to such effect.

Respectfully submitted,

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I hereby certify that this correspondence is being facsimile transmitted to the USPTO 703.308.4242 addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on Thursday, February 06, 2003.

Signature

chemokines such as MIP-1a, MCP-1 and RANTES; and treatment with immunotoxins, such as a conjugate between anti-CD3 antibody and diphtheria toxin.

Further objects, features, and advantages of the invention will be apparent from the following detailed description when taken in conjunction with the accompanying drawings.

Brief Description of the Drawings

FIG. 1A & 1B Photomicrographs of muscle sections histochemically stained for ß-galactosidase expression. Panel A represents a muscle (pronator teres) with a high level of expression; panel B represents a muscle (abductor pollicis longus) with an average level of expression. Magnification: 160X.

FIG. 2A-2C Expression of ß-galactosidase (light grey) and GFP (white) in rat muscle injected intraarterially at different times with the respective expression pDNAs. Panel A (640X magnification) is a low-power field illustrating that expression of ß-galactosidase and GFP were typically not co-localized. Panels B and C are high power fields (1600X magnification) that show an example of co-localization (B) and separate expression (C).

FIG. 3A-3C Muscle sections obtained 5 min (A and B) and 1 h (C) after 50 µg of Rh-pDNA in 10 ml of normal saline were injected within 7 sec into the femoral artery of rat without impeding the outflow (A) or impeding outflow (B and C). Arrows indicate Rh-pDNA between cells and arrowheads indicate pDNA inside myofibers. Magnification: 1260 X.

Detailed Description

We have found that an intravascular route of administration allows a polynucleotide to be delivered to a parenchymal cell in a more even distribution than direct parenchymal injections. The efficiency of polynucleotide delivery and expression is increased by increasing the permeability of the tissue's blood vessel. Permeability is increased by one or more of the following: increasing the intravascular hydrostatic (physical) pressure, delivering the injection fluid rapidly (injecting the injection fluid rapidly), using a large injection volume, inhibiting vessel fluid flow, and increasing permeability of the vessel wall. Prior to

chemokines such as MIP-1a, MCP-1 and RANTES; and treatment with immunotoxins, such as a conjugate between anti-CD3 antibody and diphtheria toxin.

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